Feb. 12, 1974 D. WASSERMAN ET AL 3,792,010

PLASTICIZED POLYESTER SUTURES

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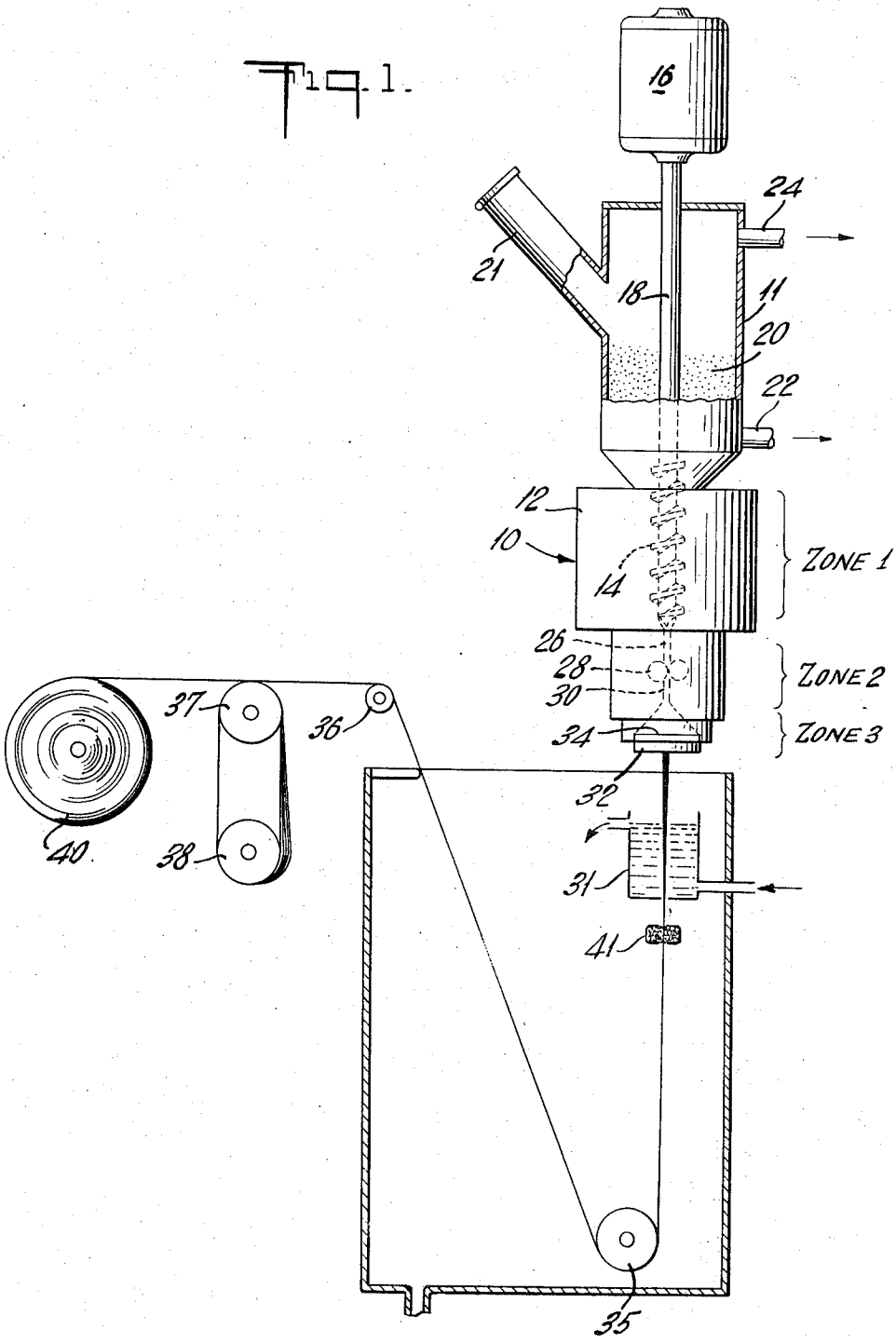
Fig. 1.



PLASTICIZED POLYESTER SUTURES

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Fig. 2.

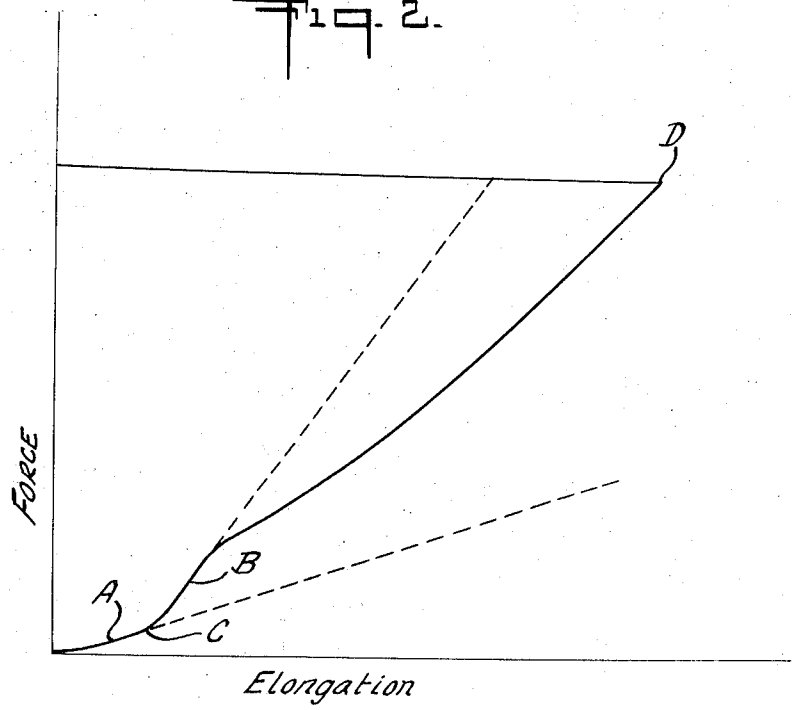
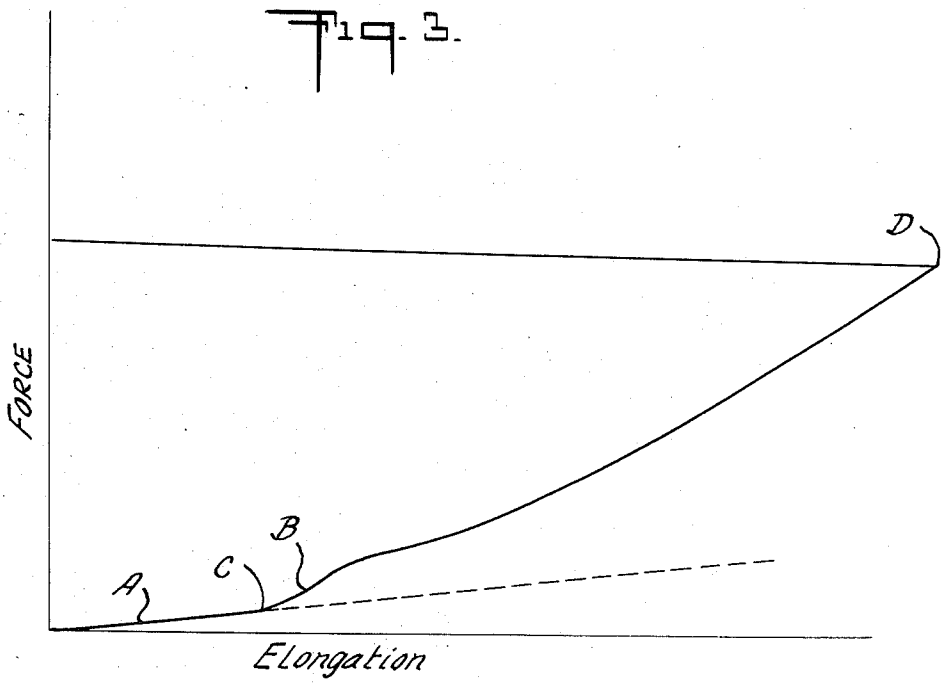


Fig. 3.



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PLASTICIZED POLYESTER SUTURES

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U.S. Cl. 260—32.2 R 4 Claims

ABSTRACT OF THE DISCLOSURE

A poly [L(—) lactide-co-glycolide] obtained by polymerizing from 10 to 15 mol percent of L(—) lactide and from 85 to 90 mole percent of glycolide is plasticized with from about 10 weight percent to about 15 weight percent of bis-2-methoxyethyl phthalate and extruded to form flexible monofilaments that are sterilized with ethylene oxide. The sterile monofilament sutures have a straight tensile strength of about 65,000 to 72,000 p.s.i.; and a Young's modulus of from about 4.5×10^5 p.s.i. to about 6.8×10^5 p.s.i. The sutures retain up to about 37 percent of their original tensile strength for fifteen days when implanted in living animal tissue.

BACKGROUND OF THE INVENTION

This invention relates to the surgical repair of body tissue and more particularly to the suturing of body tissue with new and improved absorbable surgical sutures prepared from plasticized copolymers of glycolide and L(—) lactide.

Catgut monofilaments (collagen derived from beef or sheep intestines) are the most commonly-used absorbable sutures on the market. Collagen sutures are also manufactured by extruding acid-swollen collagen fibrils derived from beef tendon into a dehydrating bath to form filaments that are stretched to further orient the collagen fibrils and cohered to form a strand. The manufacture of reconstituted collagen sutures is described in U.S. Pats. No. 3,114,373 and No. 3,114,593.

Absorbable sutures may also be manufactured from a polyglycolide homopolymer as described in U.S. Pat. No. 3,297,033. It is a disadvantage of polyglycolide homopolymer monofilaments, however, that they are extremely stiff and difficult for the surgeon to tie, particularly in the larger sizes, i.e., size 2/0. Although the handling characteristics of a suture are difficult to define, a suture should not be wiry or stiff and should remain in the position in which it is placed until moved by the surgeon.

It is another disadvantage of polyglycolide homopolymer monofilaments that they exhibit memory and will tend to retain the shape of the package. Stated in another way, a polyglycolide monofilament that is packaged as a coil will, to a large extent, retain the coil form after removal from the package. This makes it difficult for the surgeon to handle and tie down the monofilament particularly in the large sizes.

Yet another disadvantage of the polyglycolide monofilaments is that they rapidly lose tensile strength when implanted in animal tissue. While this rapid loss of tensile strength can be improved somewhat by annealing under the conditions defined in U.S. Pat. No. 3,422,181, the annealed monofilaments are still too stiff for wide acceptance by the surgeon.

To improve the handling characteristics of polyglycolide homopolymer sutures, such products are presently being manufactured in the form of a braided multifilament. It is well known that braided sutures have an acceptable hand and they are preferred by some surgeons because they have superior knotting characteristics relative to monofilaments. However, the high temperature that is required to extrude the low denier multifilaments will unavoidably result in some thermal degradation of the polyglycolide homopolymer. Moreover, many surgeous prefer to use a monofilament suture in infected areas.

Attempts to plasticize the polyglycolide homopolymer thereby improving the flexibility and hand of extruded monofilaments while retaining the advantages of the monofilament structure have not been successful because of the insolubility of polyglycolide homopolymer and its incompatability with known plasticizers. Polyglycolide homopolymer is immiscible with known plasticizers and attempts to extrude a plasticized monofilament has resulted in separation of the plasticizer from the polyglycolide.

These problems have been resolved by the present invention which enables one to manufacture absorbable monofilament sutures of satisfactory tenacity and knot strength while retaining the percent elongation, flexibility, and absorption characteristics that are demanded by the surgeon.

SUMMARY OF THE INVENTION

It has now been discovered that a stable plasticized poly [L(—) lactide-co-glycolide] may be prepared by reacting with glycolide, in the presence of as much as 10 to 15 percent by weight bis-2-methoxyethyl phthalate from about 10 mol percent to about 15 mol percent L(—) lactide. Similar amounts of other non-toxic polar plasticizers that are compatible with the poly [L(—) lactide-co-glycolide] such as acetoxy triethyl citrate may be substituted for the bis-2-methoxyethyl phthalate.

Monofilaments extruded from such plasticized poly [L(—) lactide-co-glycolide] compositions have an excellent hand and a straight tensile strength after sterilization of about 65,000 p.s.i. to 72,000 p.s.i. As much as 37 percent of the original tensile strength of the suture is retained for fifteen days after implantation in animal tissue. This advantage of retaining a large portion of the original tensile strength after fifteen days implantation in living tissue appears to be characteristic of the high glycolide copolymer compositions and is particularly outstanding in the case of the 10 mol percent L(—) lactide/90 mol percent glycolide copolymer composition as will be shown by the examples and data presented below.

As indicated above, a stiff or wiry suture is difficult for the surgeon to handle and tie down. A flexible suture by contrast has a "dead" quality and may be characterized by the surgeon as "throwable." Fortunately, the hand of the monofilament suture can be related to certain physical characteristics that will enable one to predict its acceptability to the surgeon independent of such subjective parameters as throwability, deadness, flexibility, or hand.

Physical characteristics of monofilament sutures that may be directly related to the ease of handling by the surgeon are Young's modulus, which is a measurement of flexibility; plastic flow, which is a measure of extendability; yield stress data and the percent elongation at the breaking point. These properties are an indication of the acceptability of a monofilament to the surgeon. The method of determining these characteristics and their correlation with pliability are described below.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will appear more clearly from the following detailed description when taken in connection with the following drawings which show by way of example a preferred embodiment of the inventive idea.

In the drawings:

FIG. 1 illustrates apparatus for extruding and drawing the plasticized sutures of the present invention.

FIG. 2 is a reproduction of a stress-strain curve, obtained by applying stress at a constant rate to a plasticized poly [L(—) lactide-co-glycolide] monofilament suture

that has been produced in accordance with the present invention.

FIG. 3 is a reproduction of a stress-strain curve, obtained by applying stress at a constant rate to a poly [L(—) lactide-co-glycolide] monofilament suture.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The composition for the manufacture of plasticized poly [L(—) lactide-co-glycolide] monofilament sutures described herein is a copolymer obtained by reacting no less than 10 mol percent and no more than 15 mol percent L(—) lactide in the presence of no less than 85 mol percent and no more than 90 mol percent glycolide.

Both the L(—) lactide and the glycolide used in the polymerization reaction should be pure and dry. The reaction is run in a dry container under a blanket of dry nitrogen. Stannous octoate is used to catalyze the polymerization. The ratio of monomer to catalyst (mole/mole) is desirably in the range of about 25,000–150,000:1. A minor quantity of glycolic acid may be present to control the molecular weight. The ratio of monomer to glycolic acid is in the range of 400:1 to 4,000:1. The plasticizer, 10 to 15 percent by weight, is preferably added to the reaction flask prior to polymerization.

To effect polymerization, the mixture of L(—) lactide plasticizer and glycolide is heated at a temperature of about 200° C. for about five hours.

If the plasticized copolymer is to be used in the manufacture of colored sutures, the dye (0.1 percent to 0.5 percent by weight D&C Violet No. 2) is added to the reaction flask prior to polymerization. D&C Violet No. 2 is 1-hydroxy-4-p-toluinoanthraquinone. This dye is uniformly dispersed throughout the reaction mixture and has little adverse effect on the polymerization reaction. Following the polymerization reaction, the dyed and plasticized polymer composition may be extruded into air to form a monofilament which is drawn and annealed prior to sterilization.

The apparatus used to extrude the copolymer compositions of the present invention is illustrated in FIG. 1, which drawing should be referred to for an understanding of the physical steps involved in extruding the copolymer to form a multifilament. The extruder **10** that is used to form the multifilament has a hopper **11** supported in a vertical plane and communicating at its lower end with a cylindrical barrel **12**. A screw **14** slightly smaller in diameter than the barrel **12** is mounted for rotation therein and is driven by a variable-speed motor **16** through the shaft **18**.

A finely-divided plasticized poly [L(—) lactide-co-glycolide] composition **20** to be extruded is transferred into the hopper through a side arm **21** under dry nitrogen and moisture is excluded from the extruder by a continuous flow of dry nitrogen which enters the hopper through the port **22** and exits through the port **24**.

To complete the description of the extrusion step, the finely-divided plasticized poly [L(—) lactide-co-glycolide] flows from the bottom of the hopper into the cylindrical barrel of the extruder where it is melted and forced by the screw through a bore **26** into the chamber of a gear pump **28**. The gear pump is rotated by a variable-speed motor (not shown) to meter the molten copolymer through a bore **30** to a die **32**. Immediately preceding this die is a filter screen **34**.

The extrusion die is constructed with a long land length and a single orifice. Preferably, the die orifice has an entrance angle of about 20°. With this entrance angle, a streamlined flow is obtained insuring uniform extrudate.

During the operation of the extruder described above, the temperature of the screw (Zone **1**) the gear metering pump (Zone **2**) and the die (Zone **3**) is continuously controlled by three electric heating units which surround the screw, metering pump, and die respectively. In addition, provision is made to continuously monitor the pressure applied to the molten copolymer by the screw **14** and by the metering pump **28**.

In extruding the plasticized copolymers described in the examples which follow, the dried copolymer powder is placed in the hopper **11** and flows by gravity into the barrel **12** of the extruder. The screw **14** conveys the polymer through Zone **1** where it is melted and forces the molten polymer at pressures as high as 2,000 p.s.i. through the port **26** into gear pump **28** which meters the volume of material passing through the die **32**. The temperature of the melted copolymer is controlled as it passes through the metering pump (Zone **2**) and extrusion die (Zone **3**).

In normal operation, the screw (Zone **1**) is maintained at about 240°–245° C.; the metering pump (Zone **2**) between 195° C. and 210° C.; and the die (Zone **3**) between 195° C. and 215° C. The extruded monofilament **33** is quenched in a water bath **31** at room temperature.

The monofilament passes through the bottom of the water bath, past the sponges **41**, around the idler **35**, over roller **36**, and is wrapped around the godets **37** and **38**, to prevent any slipping that could result in variations in the stretch occurring between the die face and the idler **35**. The monofilament from the godet **37** is taken up on a take-up drum **40**.

As indicated above, the monofilament **33** may be stretched and annealed before sterilization. The monofilament suture may be sterilized with little decrease in tensile strength by exposing the suture to a wet atmosphere of Freon and ethylene oxide.

The tensile strength and percent elongation at break reported in Examples I through XI are determined by A.S.T.M. Method D–2256–66T using a constant rate of extension tester, namely a table model Instron Universal Testing Instrument manufactured by the Instron Corporation of Canton, Mass. This test method is described in the 1966 Book of A.S.T.M. Standards, Part 24 (published in August of 1966 by the American Society for Testing Material, 1916 Race St., Philadelphia, Pa). The 20 seconds to break is approximated by using a two-inch sample (or gauge length) with the Instron Tester cross-head speed set at two inches per minute.

All viscoelastic measurements reported in the tables are made on a table model Instron Tensile Tester using a Type C Tension Cell; full-scale range 1 to 10 pounds. The measurements are made in an air-conditioned laboratory at 72° F. and 50% relative humidity. To hold the specimen suture strand, two line contact jaws are used. The diameter of the strand is measured to 0.0001 inch and the area of the strand is calculated. A 2-inch samples is placed between the rubber-faced jaws and both jaws closed, by hand to prevent slippage of the filament. The strand is elongated at a constant rate until it breaks. The Instron machine is operated at a crosshead speed of 2 inches per minute and a chart speed of 10 inches per minute.

It has been noted that the pliability of a plasticized poly [L(—) lactide-co-glycolide] suture may be correlated with its behavior under stress. Physical tests that may be used to reliably evaluate the subjective characteristics of "hand," flexibility, and extensibility are described in Example I.

The present invention will be further illustrated by the following examples which describe the manufacture of plasticized monofilament poly [L(—) lactide-co-glycolide] sutures all of which retain at least 19 percent of their original tensile strength for fifteen days after implantation in animals.

Throughout the specification and examples which follow, all quantities are expressed in parts by weight unless otherwise indicated.

EXAMPLE I

Preparation of poly [L(−) lactide-co-glycolide] from 15 mol percent L(−) lactide and 85 mol percent glycolide containing 10 parts per hundred bis-2-methoxyethyl phthalate (1023–164)

A 1-liter stainless-steel reactor vessel equipped with a stirrer paddle, stirrer motor, and gas outlet is heated to 110° C. under vacuum to remove moisture from the interior surfaces of the vessel.

A mixture of 89.3 g. (0.62 mole) of pure L(−) lactide, M.P. 97–99° C. (specific rotation at least 282° C.) and 406.0 g. (3.5 moles) of pure glycolide, M.P. 82.5–84.5° C. is prepared using dry glassware in a dry nitrogen glove box. This mixture of 15 mol percent L(−) lactide and 85 mol percent glycolide is transferred to the reactor vessel under a blanket of nitrogen. To this reaction mixture is added 42.62 ml. (49.53 g.) of bis-2-methoxyethyl phthalate and 0.50 ml. of a 0.33 molar catalyst solution containing 13.41 g. of stannous octoate in 100 ml. of toluene (1.65×10^{-4} moles) using a dry glass syringe. The molar ratio of monomer to catalyst is 25,000:1. Then 0.1566 g. (2.06×10^{-3} moles) of glycolic acid is added. The molar ratio of monomer to glycolic acid is 2,000:1.

The reactor vessel is closed and a high vacuum (0.1–0.2 mm. of mercury pressure) is applied to remove the toluene. The vessel is purged with dry nitrogen by evacuating and releasing the vacuum twice with the gas. The vessel is then again filled with dry nitrogen until the pressure within the vessel is about one pound above atmospheric pressure and the outlet valve is closed.

The vessel and its contents are lowered into a silicone bath, pre-heated to a temperature of 185° C. and heated with stirring at that temperature for 40 minutes. The stirrer is raised above the liquid and the heating at 185° C. is continued for an additional 4 hours and 20 minutes. The unit is cooled and the polymer mass is removed from the opened unit. This is chilled with Dry Ice, cut in quarters with a hand saw, ground with Dry Ice in a Cumberland Mill and dried in vacuo for 48 hours at 0.1 mm. and 25° C. The yield of copolymer obtained (product 1023–164) is 78%. The copolymer so obtained has a transition temperature (softens) in the range of 180–185° C.; a tack point of 191° C.; a draw point of 197° C.; and a melting point (flow) of 205° C. The inherent viscosity of this copolymer at 0.1% concentration in hexafluoroisopropanol at 25° C. is 1.40 (corrected). The melt index of an aliquot sample of the plasticized copolymer is determined by a procedure similar to ASTM Method D1238–65T published by the American Society for Testing Materials, 1916 Race St., Philadelphia, Pa. 19103; using an extrusion plastometer (melt indexer) manufactured by Tinius Olsen Testing Machine Co., Easton Road, Willow Grove, Pa. 19090. The melt index at 215° C. using a 3,800 g. weight and a 25 mil. orifice is 1.25 (grams/10 minutes at 900 seconds).

EXAMPLE II

Extrusion of plasticized poly [L(−) lactide-co-glycolide] (1038–86)

The plasticized copolymer (1023–164) described in Example I above is extruded under dry nitrogen using a screw extruder of the type illustrated in FIG. 1 to produce a monofilament. Three 80-mesh screens (U.S. Standard) are placed between the metering pump and the die **32**. The die used has a single orifice 40 mils in diameter.

The screw of the extruder is operated to maintain a pressure of 1,500 p.s.i. and the metering pump is operated to maintain a pressure at the die of 100–500 p.s.i., the rate of extrusion being 55 grams per hour.

Throughout the extrusion, the screw feed section of the extruder, Zone **1**, is maintained at 240° C.; the temperature of the metering pump, Zone **2**, is 205° C.; and the die temperature, Zone **3**, is maintained at 205° C. The monofilament is collected on the take-up spool **50** at the rate of 11.5 feet per minute.

The extruded monofilament was conditioned on the spool by heating for one-half hour at 65° C., then drawn 4× in a glycerin bath maintained at 107° C. (1001–193). After the drawing step, the drawn monofilament is wound on a rack under tension and the rack is immersed in bis-2-methoxyethyl phthalate maintained at 120° C. for 24 hours (1001–196).

EXAMPLE III

Sterilization and packaging of 15/85 poly [L(−) lactide-co-glycolide] sutures containing 10 parts per hundred bis-2-methoxyethyl phthalate (1001–207)

The stretched and annealed monofilament described in the preceding Example II is cut into lengths suitable for suture use and sterilized with ethylene oxide in open vent packages, by exposing the sutures to an atmosphere of Freon and ethylene oxide (500 mg. of ethylene oxide per liter of gas) at 70% relative humidity and 38° C. for 6 hours.

The packages of sterilized monofilament sutures (diameter 9.7 mils) are sealed to maintain sterility until use. The sterile packaged sutures have a straight tensile strength of 4.8 lbs. (65,000 p.s.i.).

The absorption characteristics of this product (tensile strength retention in rats at the end of five days) is determined by implanting ten samples in five different animals. In like manner, the tensile strength retention is determined 10, 15, and 21 days post implantation. The average of ten breaks using an Instron Testing Machine operating at a cross-head speed of 1 inch per minute on a 0.5-inch sample is tabulated below:

	Days implantation				
	0	5	10	15	21
Straight tensile strength in pounds	4.8	4.1	3.0	1.2	0
Percent tensile strength retention		89	65	25	0

Stress-strain curves produced with the sterile monofilaments of this example on a table model Instron Tensile Tester using a Type C Tension Cell; full-scale range 1–10 lbs. have the general shape illustrated in FIG. 2. Young's modulus (p.s.i.$\times10^5$) is the initial modulus as determined from the slope of the curve A of FIG. 2. Young's modulus is the ratio of applied stress to strain in the elastic region and measures the elastic component of a suture's resistance to stress. This value is related to the flexibility of a suture.

Plastic flow (p.s.i.$\times10^5$) is the viscoelastic modulus as determined from the slope of the curve B of FIG. 2. It measures the plastic component of a suture's resistance to stress and is related to the "give" a suture exhibits under a force in excess of the yield stress.

The yield stress (p.s.i.$\times10^4$) is the first point of inflection in the stress-strain curve or the point of intersection C of the slopes A and B of FIG. 2. Yield stress measures the force required to initiate viscoelastic flow and is related to the straightenability of a suture.

The Young's modulus of the monofilament sutures described in this Example III is $4.5\pm0.6\times10^5$.

EXAMPLE IV

Preparation of a poly [L(−) lactide-co-glycolide] from 10 mol percent L(−) lactide and 90 mol percent glycolide plasticized with 15 parts per hundred bis-2-methoxyethyl phthalate (1023–192)

A 1-liter stainless-steel reactor vessel equipped with a stirrer paddle, stirrer motor, and gas outlet is heated to 110° C. under vacuum to remove moisture from the interior surfaces of the vessel.

A mixture of 56.16 g. (0.39 mole) of pure L(−) lactide, M.P. 97–99° C. (specific rotation at least 282° C.) and 406 g. (3.5 moles) of pure glycolide, M.P. 82.5°–84.5° C. is prepared using dry glassware in a dry nitrogen

glove box. This mixture of 10 mol percent L(−) lactide and 90 mol percent glycolide is transferred to the vessel under a blanket of dry nitrogen. To this reaction mixture is added 59.66 ml. (69.32 g.) of bis-2-methoxyethyl-phthalate, 0.47 ml. of a 0.33 molar catalyst solution containing 13.41 g. of stannous octoate in 100 ml. of toluene (1.56×10^{-4} moles) using a dry glass syringe. The molar ratio of monomer to catalyst is 25,000:1. Then 0.1478 g. (1.94×10^{-3} moles) of glycolic acid is added. The molar ratio of monomer to glycolic acid is 2,000:1.

The reaction vessel is closed and a high vacuum (0.1–0.2 mm. of mercury pressure) is applied to remove the toluene. The vessel is purged with dry nitrogen by evacuating and releasing the vacuum twice with the gas. The vessel is then again filled with dry nitrogen until the pressure within the vessel is about one pound above atmospheric pressure and the outlet valve is closed.

The vessel and its contents are lowered into a silicone bath, pre-heated to a temperature of 185° C. and heated with stirring at that temperature for fifty minutes. The stirrer is raised above the liquid *and* the heating at 185° C. is continued for four hours and thirty minutes longer. The unit is cooled and the polymer mass is removed from the opened unit. This is chilled with Dry Ice, cut in quarters with a hand saw, ground with Dry Ice in a Cumberland Mill and dried in vacuo for 48 hours at 0.1 mm. and 25° C. The yield of copolymer obtained is 473 g. This product has a transition temperature (softens) in the range of 190–192° C.; a tack point of 199° C.; a draw point of 205° C.; and a melting point (flow point) of 209° C. The inherent viscosity of this copolymer at 0.1% concentration in hexafluoroisopropanol at 25° C. is 1.62 (corrected).

The melt index of this plasticized copolymer as determined by the method described in Example I above is 2.21.

EXAMPLE V

Extrusion of 10–90 poly [L(−) lactide-co-glycolide] containing 15 parts per hundred bis-2-methoxyethyl phthalate (1038–90)

The plasticized copolymer (1023–192) described in Example IV is extruded as described in Example II through a 37 mil orifice to produce a monofilament. One of the 80-mesh screens before the die was replaced by two 100-mesh screens.

The screw of the extruder is operated to maintain a pressure of 1,500 p.s.i. and the metering pump is operated to maintain a pressure at the die of 50–150 p.s.i., the rate of extrusion being 55 grams per hour.

Throughout the extrusion, the screw feed section of the extruder, Zone **1**, is maintained at 240° C.; the temperature of the metering pump, Zone **2**, is 195° C.; and the die temperature, Zone **3**, is maintained at 195° C. The monofilament is collected on the take-up spool **50** at the rate of 11 feet per minute.

The extruded monofilament is stretched and annealed (1001–202) as described above in Example II and sterilized as described in Example III (1001–208).

The packages of sterilized monofilament sutures (diameter 9.6 mils) are sealed to maintain sterility until use. The sterile-packaged sutures have a straight tensile strength of 5.2 lbs. (72,000 p.s.i.). The Youn's modulus, determined as described above in Example III is

$$6.3\pm0.8\times105$$

The absorption characteristics of this product (tensile strength retention in rats at the end of five days) is determined by implanting ten samples in five different animals. In like manner, the tensile strength retention is determined 10, 15, and 21 days post implantation. The average of ten breaks using an Instron Testing Machine operating at a cross-head speed of 1 inch per minute on a 0.5-inch sample is tabulated below and illustrated in FIG. 2.

	Days implantation				
	0	5	10	15	21
Straight tensile strength in pounds	5.2	4.2	3.4	1.9	------
Percent tensile strenth retention		81	65	37	------

EXAMPLE VI

Preparation of a poly [L(−) lactide-co-glycolide] from 10 mol percent lactide and 90 mol percent glycolide containing 10 parts per hundred bis-2-methoxyethyl phthalate (1023–160)

A 1-liter stainless-steel reactor vessel equipped with a stirrer paddle, stirrer motor, and gas outlet is heated to 110° C. under vacuum to remove moisture from the interior surfaces of the vessel. A mixture of 56.16 g. (0.39 mole) of pure L(−) lactide, M.P. 97–99° C. (specific rotation at least 282° C.) and 406.0 g. parts (3.5 moles) of pure glycolide, M.P. 82.5–84.5° C. is prepared using dry glassware in a dry nitrogen glove box. This mixture of 10 mol percent L(−) lactide and 90 mol percent glycolide is transferred to the vessel under a blanket of nitrogen. To this reaction mixture is added 39.8 ml. (46.2 g.) bis-2-methoxyethyl phthalate and 0.47 ml. of a 0.33 molar catalyst solution containing 13.41 g. of stannous octoate in 100 ml. of toluene (1.56×10^{-4} moles) using a dry glass syringe. The molar ratio of monomer to catalyst is 25,000:1. Then 0.148 g. (1.94×10^{-3} moles) of glycolic acid is added. The molar ratio of monomer to glycolic acid is 2,000:1.

The reaction vessel is closed and a high vacuum (0.1–0.2 mm. of mercury pressure) is applied to remove the toluene. The vessel is purged with dry nitrogen by evacuating and releasing the vacuum twice with the gas. The vessel is then again filled with dry nitrogen until the pressure within the vessel is about one pound above atmospheric pressure and the outlet valve is closed. The vessel and its contents are lowered into a silicone bath, preheated to a temperature of 185° C. and heated with stirring at that temperature for 45 minutes. The stirrer is raised above the liquid and the heating at 185° C. is continued for 4 hours and 15 minutes. The unit is cooled and the copolymer mass is removed from the opened unit. The copolymer is chilled with Dry Ice, cut in quarters with a hand saw, ground with Dry Ice in a Cumberland Mill to pass through a 3/16-inch screen and de-metallized with a magnet. The ground copolymer is dried in vacuo for 48 hours at 0.1 mm. and 25° C. The copolymer so obtained has a transition temperature (softening point) in the range of 189–192° C.; a tack point of 197° C.; a draw point of 207° C.; and a melting point of 211° C.

The inherent viscosity of this plasticized copolymer at 0.1% concentration in hexafluoroisopropanol at 25° C. is 1.38 (corrected).

The melt index of the plasticized copolymer determined as described above in Example I is 1.95.

EXAMPLE VII

Extrusion of 10–90 poly [L(−) lactide-co-glycolide] containing 10 parts per hundred bis-2-methoxyethyl phthalate (1038–85)

The polymer (1023–160) described in Example VI is extruded using a screw extruder of the type illustrated in FIG. 1, to produce a monofilament. A filter of three 80-mesh screens (U.S. Standard) are placed between the metering pump **28** and the die **32**. The die used has a single orifice 40 mils in diameter.

The screw of the extruder is operated to maintain a pressure of 1,500 p.s.i. and the metering pump is operated to maintain a pressure at the die of 50 p.s.i., the rate of extrusion being 55 grams per hour.

Throughout the extrusion, the screw feed section of the extruder, Zone **1**, is maintained at 245° C.; the temperature of the metering pump, Zone **2**, is 210° C.; and

the die temperature, Zone 3, is maintained at 215° C. The monofilament is collected on the take-up spool 50 at the rate of 11.5 feet per minute.

The monofilament so obtained is conditioned, drawn, and annealed under tension as described in Example II above.

The stretched and annealed monofilaments (1001–192) are cut into lengths suitable for suture use and sterilized with ethylene oxide in open vent packages, by exposing the sutures to an atmosphere of Freon and ethylene oxide (500 mg. of ethylene oxide per liter of gas) at 70 percent relative humidity and 38° C. for 6 hours (1001–206).

The packages of sterilized sutures are sealed to maintain sterility until use. The sterile-packaged sutures (diameter 9.6) have a straight tensile strength of 4.8 lbs. (66,300 p.s.i.). The Young's modulus, determined as described above in Example III is $6.8 \pm 1.1 \times 10^5$.

The absorption characteristics of this product (tensile strength retention in rats at the end of five days) is determined by implanting ten samples in five different animals. In like manner, the tensile strength retention is determined 10, 15, and 21 days post implantation. The average of ten breaks using an Instron Testing Machine operating at a cross-head speed of 1 inch per minute on a 0.5-inch sample is tabulated below.

	Days implantation				
	0	5	10	15	21
Straight tensile strength in pounds	4.8	3.9	2.9	0.9	0
Percent tensile strength retention		89	66	19	

EXAMPLE VIII

Preparation of a 15–85 poly [L(—) lactide-co-glycolide] (1078–45)

A 1-liter stainless-steel reactor vessel equipped with a stirrer paddle, stirrer motor, and gas outlet is heated to 110° C. under vacuum to remove moisture from the interior surfaces of the vessel. A mixture of 126.7 g. (0.88 mole) of pure L(—) lactide, M.P. 97–99° C. (specific rotation at least 282° C.) and 580 parts (5.0 moles) of pure glycolide is prepared using dry glassware in a dry nitrogen glove box. This mixture of 15 mol percent L(—) lactide and 85 mol percent glycolide is transferred to the vessel under a blanket of nitrogen. To this reaction mixture is added 36 ml. of a 0.33 mole catalyst solution containing 13.41 g. of stannous octoate in 100 ml. of toluene (1.18×10^{-4} moles) using a dry glass syringe. Then 0.1397 g. (1.8×10^{-3} moles) glycolic acid is added. The molar ratio of monomer to catalyst is 50,000:1 and the molar ratio of monomer to glycolic acid is 3,200:1.

The vessel is closed and a high vacuum (0.1–0.2 mm. of mercury pressure) is applied to remove the toluene and ether. The vessel is purged with dry nitrogen by evacuating and releasing the vacuum twice with the gas. The vessel is then again filled with dry nitrogen until the pressure within the vessel is about one pound above atmospheric pressure and the outlet valve is closed. The vessel and its contents are lowered into a silicone bath, pre-heated to a temperature of 200° C. and heated with stirring at that temperature for 40 minutes. The stirrer is raised above the liquid and the heating at 200° C. is continued for four hours and 20 minutes. The unit is cooled and the polymer mass is removed from the opened unit. This is chilled with Dry Ice, cut in quarters with a hand saw, ground with Dry Ice in a Cumberland Mill and dried in vacuo for 48 hours at 0.1 mm. and 25° C. The copolymer so obtained has a tack point of 201° C.; a draw point of 212° C. and a melting point of 228° C.

The inherent viscosity of this copolymer at 0.1% concentration in hexafluoroisopropanol at 25° C. is 1.74. The melt index of this copolymer determined by the method described in Example I above is 0.219.

EXAMPLE IX

Extrusion of 15–85 poly[L(—)lactide-co-glycolide] (1038–188)

The copolymer (1078–45–B1) described in Example VIII is extruded as described in Example V to produce a monofilament. The screw of the extruder is operated to maintain a pressure of 2,000 p.s.i. and the metering pump is operated to maintain a pressure at the die of 550–1,150 p.s.i., the rate of extrusion being 48 grams per hour.

Throughout extrusion, the screw feed section of the extruder, Zone 1, is maintained at 245° C.; the temperature of the meaning pump, Zone 2, is 205° C. and the die temperature, Zone 3, is maintained at 205° C. The monofilament is collected on the take-up spool 50 at the rate of 9 feet per minute.

The extruded monofilament was conditioned and drawn as described in Example II and annealed on a rack under tension for 24 hours at 120° C. (1088–55).

The stretched and annealed monofilaments are cut into lengths suitable for suture use and sterilized with ethylene oxide in open vent packages, by exposing the sutures to an atmosphere of Freon and ethylene oxide (500 mg. per liter of gas) at 70% relative humidity and 38° C. for 6 hours.

The packages of sterilized sutures (1088–67) are sealed to maintain sterility until use. The sterile-packaged sutures (diameter 9.9 mils) have a straight tensile strength of 88,000 p.s.i. The Young's modulus, determined as described above in Example III and illustrated in FIG. 3 is 10.6×10^5.

EXAMPLE X

Preparation of a poly[L(—)lactide-co-glycolide] from 10 mol percent lactide and 90 mol percent glycolide (1094–98)

A 10–90 poly[L(—)lactide-co-glycolide] is prepared by the procedure described in Example IX above, in a 1.5 gallon jacketed reactor fitted with a heavy-duty stirrer using 374 g. (2.6 moles) of L(—)lactide; 2668 g. (23 moles) of glycolide; 1.56 ml. of a 0.33 molar catalyst solution containing 13.41 g. of stannous octoate in 100 ml. of toluene (5.12×10^{-4} moles); 2.432 g. (3.2×10^{-2} moles) of glycolic acid and 6.1 g. (0.2 weight percent) D&C Violet No. 2 dye. The molar ratio of monomer to catalyst is 50,000:1, and the molar ratio of monomer to glycolic acid is 800:1. Reactants are heated from 72° C. (starting temperature) to 200° C. over 50 minutes and stirred at 14–30 r.p.m. during the period of polymerization. The heat of the polymerization reaction causes the temperature to rise to 226° C. about one hour after the reaction starts, and drops to 212° at the end of the reaction (after 4 hours).

The resulting copolymer has a transition temperature (softening point) of 185° C.; a tack point of 193° C.; a draw point of 200° C.; and a melting point of 205° C.

The inherent viscosity of this copolymer at 0.1 percent concentration in hexafluoroisopropanol at 25° C. is 1.43.

The melt index of the copolymer determined as described above in Example I is 0.64.

EXAMPLE XI

Extrusion of 10/90 poly[L(—)lactide-co-glycolide] (1038–189)

The copolymer (1094–98) described in Example X above is extruded under dry nitrogen using a screw extruder of the type illustrated in FIG. 1 to produce a monofilament. The filter described in Example V is placed between the metering pump and the die 32. The die used has a single orifice 37 mils in diameter.

The screw of the extruder is operated to maintain a pressure of 2,000 p.s.i. and the metering pump is operated to maintain a pressure at the die of 750–900 p.s.i., the rate of extrusion being 46 grams per hour.

Throughout the extrusion, the screw feed section of the extruder, Zone 1, is maintained at 245° C.; the temperature of the metering pump, Zone 2, is 205° C.; and the die temperature, Zone 3, is maintained at 205° C. The monofilament is collected on the take-up spool 50 at the rate of 9 feet per minute.

The extruded monofilament was conditioned 1 hour at 65° C. and drawn 4× in a glycerin bath at 107° C. (1088–56). After the drawing step, the drawn monofilament is wound on a rack under tension and annealed for 24 hours at 120° C. in an atmosphere of dry nitrogen (1088–59). The monofilament strands are then sterilized and packaged as described above in Example III.

The sterile packaged sutures (1088–66) (diameter 9.4 mils) have a tensile strength of 94,000 p.s.i. and a Young's modulus of 11.05×10^5 p.s.i.

What is claimed is:

1. A sterile plasticized poly [L(—) lactide-co-glycolide] monofilament suture; obtained by polymerizing from about 10 mol percent to about 15 mol percent L(—) lactide with from about 90 mol percent to about 85 mol percent glycolide; and plasticized with from about 10 parts per hundred to about 15 parts per hundred of bis-2-methoxyethyl phthalate; said suture being characterized by a straight tensile strength of at least 65,000 p.s.i. and a Young's modulus of from about 4.5×10^5 p.s.i. to about 6.8×10^5 p.s.i.

2. The sterile plasticized poly [L(—) lactide-co-glycolide] monofilament suture of claim 1, obtained by polymerizing about 15 mol percent L(—) lactide with about 85 mol percent glycolide and plasticized with about 10 parts per hundred of bis-2-methoxyethyl phthalate.

3. The sterile plasticized poly [L(—) lactide-co-glycolide] monofilament suture of claim 1 obtained by polymerizing about 10 mol percent L(—) lactide with about 90 mol percent glycolide and plasticized with about 15 parts per hundred of bis-2-methoxyethyl phthalate.

4. The sterile plasticized poly [L(—) lactide-co-glycolide] monofilament suture of claim 1, obtained by polymerizing about 10 mol percent L(—) lactide with about 90 mol percent glycolide and plasticized with about 10 parts per hundred of bis-2-methoxyethyl phthalate.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,792,010 Dated February 12, 1974

Inventor(s) David Wasserman & Alan J. Levy

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In Column 4, line 54, "samples" should read --- sample ---.

In Column 7, line 63, "youm's" should read --- young's ---.

In Column 7, line 65, "X105" should read --- $X10^5$ ---.

In Column 10, line 13, "meaning" should read --- metering" ---.

In Column 12, line, "reference to Birten 3,126,355 is missing".

Signed and sealed this 19th day of November 1974.

(SEAL)
Attest:

McCOY M. GIBSON JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents